The Relations Between Levels of Cadmium and Thyroid Parameters in Hemodialysis Patients

Hemodiyaliz Hastalarında Tiroit Parametreleri ve Kadmiyum Düzeyleri Arasindaki İlişki

Hemodiyalizde Kadmiyum ve Tiroit Parametreleri / Cadmium and Thyroid Parametres in Hemodialysis

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Özet

Amaç: Sunulan çalışmanın amacı, hemodiyaliz ve sağlıklı kişilerde serum kadmiyum (Cd), total triiyodotironin (T3), total tiroksin (T4) ve adrenokortikotropik hormon (ACTH) düzeyleri arasında istatistiksel olarak farklılık ve de gruplar arasında bu eser element ile tiroit profilleri ve ACTH arasında korelasyon olup olmadığını değerlendirmekti. Gereç ve Yöntem: Çalışmaya 2-16 yıldır haftada en az üç kez diyalize giren, her seansı en az 4 saat olan 47 hemodiyaliz hastası (hemodiyaliz grubu) ve 23 sağlıklı kişi (kontrol grubu) dahil edildi. Hemodiyaliz grubunda kan numuneleri diyaliz öncesi ve sonrası alındı. Kontrol grubunun kan numuneleri 10 saatlik açlık sonrası alındı. Bulgular: Total T3 ($p \leq 0.001$) düzeyleri kontrol grubunda diyaliz öncesi ve diyaliz sonrasına göre daha yüksekti. Total T3 ($p \leq 0.05$) düzeyleri diyaliz öncesi diyaliz sonrasına göre daha düşüktü. Kontrol grubunda Total T4 düzeyleri yüksek, Cd düzeyleri ise düşük tespit edildi. Bu parametreler, diyaliz öncesine göre ise, istatistiksel açıdan önemli farklılık (sırasıyla $p \leq 0.001$, $p \leq 0.01$) gösterdi. ACTH düzeyleri bakımından gruplar arasında önemli bir farklılık bulunmadı. Tartışma: Hemodiyaliz hastalarında Cd düzeylerinin ölçülmesinin önemli olabileceği kanısındayız. Ancak Cd, tiroit profilleri ve ACTH düzeyleri arasında önemli bir ilişki bulamadık.

Anahtar Kelimeler

ACTH; Total T3; Total T4; Kadmiyum; Hemodiyaliz

Abstract

Aim: The aim of the present study is to determine whether there are statistically differences between hemodialysis patients and control (healthy) groups according to level of serum cadmium (Cd), total triiodothyronine (T3) and total thyroxine (T4) and adrenocorticotropin hormone (ACTH), and besides whether there are any correlation coefficients of trace element with thyroid profiles, ACTH in these groups. Material and Methods:The study included 47 hemodialysis patient who were dialyzed three times a week and each session was at least 4 hours. The duration of dialysis range were 2-16 yr. This group called as a "Hemodialyis group". Blood samples were taken before (pre-hemodialysis) and after (post-hemodialysis) hemodialysis session. "Control group" included 23 healthy volunteers with no medical problem. In control group, samples were taken after 10 hour fasting. Results: Levels of total T3 were higher in group of control than the levels of pre-hemodialysis and post-hemodialysis ($p \leq 0.001$). Total T3 levels were lower in pre-hemodialysis ($p \leq 0.05$) than those of post-hemodialysis. The highest level of total T4 and lowest level of Cd were in control group and these parameters were statistically different from the pre-hemodialysis (respectively $p \leq 0.001$, $p \leq 0.01$). We did not determine any significant differences between all groups according to data of ACTH levels. Discussion: We suggest that analyzing the levels of Cd may be useful for the hemodialysis patients. But, we did not determine a significant association between Cd and thyroid profiles and ACTH levels.

Keywords

ACTH; Total T3; Total T4; Cadmium; Hemodialysis

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Introduction

Chronic kidney disease is an important agent of morbidity and mortality all over the world. Dialysis in a patient with advanced chronic kidney disease is an important pace in medical science. During hemodialysis (HD), essential kidney functions such as the elimination of water and metabolic wastes as well as the correction of the electrolyte and acid/base state, are replaced by the artificial purification system. Elements such as Na+, K+, Ca++, Mg++, Cl–, and H+ must be kept in a rather narrow physiological range; otherwise, life-threatening events may occur[1]. The effects of trace elements in blood and dialysis fluid of patients with chronic renal failure have been extensively investigated. Several trace elements (including aluminum, cadmium, chromium, lanthanum, strontium and zinc) have been shown to accumulate in bone of uraemic patients[2-3]. On the basis of the results, the abnormal metabolism of trace metals contributes to a part of the uraemic symptoms, which is unresolved by maintenance hemodialysis[4]. Increased trace element concentrations can result from excessive homeopathic intake, administration of parenteral fluids or blood contact with contaminated dialysate[3].

Cadmium (Cd) is a toxic metal with extremely long biological half time of 15-20 years in humans. Cd exposure can cause a variety of adverse health effects which are more prominent, e.g.kidney dysfunction, lung diseases, disturbed calcium metabolism[5-6].

For the general population, the main sources of Cd exposure are diet (from contaminated water and crops grown on contaminated soil) and tobacco. Cadmium inhaled through cigarette smoke is more easily adopted by the body than cadmium in food or water. About 40–60 percent of the cadmium inhaled in smoke is absorbed into the bloodstream, as against to the 5–10 percent absorbed through foods. Chronic exposure to Cd often leads to renal dysfunction[1]. Exposure to occupational (previously or presently employed in Cd-battery production or residing in Cd-polluted areas near the battery plants) or relatively low environmental (domicile 2-10 km from a plant) levels of Cd appears to be a determinant for the development of end-stage renal disease[7]. The greatest accumulation occurs in the liver and kidneys[8].

Whereas some researchers[9] suggested significant alterations in Cd levels in hemodialysis patients, some researchers[10] confirmed that hemodialysis patients, who were dialyzed with cuprophan dialyzer, did not show any significant alterations in serum Cd concentrations.

Furthermore, patients with end stage renal disease display a variety of endocrine disturbances[11]. Mgbonyebi et al[12-13], conclude that the toxicity of Cd in adrenal functions causes hyperactivity in ACTH stimulation and expression. Besides, disturbances in thyroid function are common among patients on renal replacement therapy[14]. Chronic renal failure (CRF) affects thyroid function in multiple ways, including circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in thyroid hormone and increased iodine store in thyroid glands[15].

The most obvious abnormality observed in CRF patients is a reduction in the serum level of total triiodothyronine (T3). The serum levels of free T3 and total thyroxine (T4) are also reduced[16]. Moreover, it has been stated that if these patients developed hypothyroidism, free T4 values would fall and thyrotropin (TSH) values would rise simultaneously. Thus, free T4 and TSH levels combined can be used for the diagnosis of hypothyroidism in presence of CRF[11].

In this present study, we have purposed to determine the alterations of Cd, thyroid profiles and ACTH levels between the hemodialysis patients and healthy subjects, and besides whether there are any changes in these parameters between the groups of pre- and post-hemodialysis. Moreover, it has been aimed to find out whether there are any correlation coefficients of trace element with thyroid profiles, ACTH in these groups.

Material and Method

Patients: Study was materialized with the 2001/130 numbered approvals and financial support of the Committee of Selcuk University of Scientific Research Projects Coordination Department. Present study involved 47 hemodialysis patients (34 female, 13 male), who were treated in Polyclinic of Hemodialysis in Department of Nephrology of Medical Faculty of Selcuk University. The mean ages of the patients were 50,26±16,36 yr. All patients were dialyzed three times a week and each session was at least 4 hour. They were dialyzed with polysulfone dialyzing membrane. The duration of dialysis range were 2-16 yr. Those patients who had Hepatitis B, acute medical events, were using Al-containing drugs, were excluded in this study. This group called as “Hemodialysis Group”.

“Control Group” was composed of 23 healthy volunteers (7 female, 16 male) with the mean age 39,52±11,54 yr. Those people had no any medical problem, were not using alcohol and were not smokers.

Samples Collection: The blood samples were taken from the hemodialysis patients in their regular monthly check-up. No extra blood samples were taken from the patients for those biochemical parameters that were mentioned for this study. The blood samples were used from remains of their check-up sample. Samples were collected immediately before (pre-hemodialysis) and after the dialysis (post-hemodialysis) sessions. So that, blood samples were not randomly collected.

Samples of control group were taken after 10 hour fasting. Control group was selected from the people who were doing their ordinary check-up. For those biochemical parameters analyzing, the samples were used from remains of their check-up blood samples, extra blood samples were not taken.

Blood samples were divided into two tubes (a tube with an anticoagulant -EDTA and without an anticoagulant). The EDTA anticoagulant samples were centrifuged at 2000 rpm for 10 min at +4°C. Plasma ACTH levels were analyzed immediately after taking blood samples. ACTH levels were determined in Immulite 1000 OLYMPUS auto analyzer (BIODPC, Diagnostic Products Corporation 5700 West 96th Street Los Angeles, CA 90045-5597, USA) by using Immulite test kit (catalog no: LKAC1). Serum total T3 and total T4 concentrations were respectively determined by using Immulite test kits (catalog no: L2KT32, no: L2KT42) in Immulite 2000 OLYMPUS auto analyzer (BIODPC, Diagnostic Products Corporation 5700 West 96th Street Los Angeles, CA 90045-5597, USA). Serum samples were stored into polyethylene tubes at -85°C to analyze the levels of Cd. Cd levels were determined by inductively coupled plasma emission spectrometry (ICP-AES, Varian Australia Pty Ltd, Australia).

Statistical Analysis: Data were expressed as mean ± SE and analyzed with SPSS packet program. ANOVA test was used among groups. Student’s t-test for parametric test (TT3, TT4, Cd) and Mann-Whitney U test for nonparametric tests (ACTH) were used to between the groups. Pearson Correlation coefficients were applied to evaluate the relationship between levels of trace elements and the other parameters. The levels of statistical signifi-

cant were set at p≤0.05, p≤0.01, and p≤0.001.

Results

As it has been shown in the table, there are no differences in Cd levels between the patients of after hemodialysis and before hemodialysis group. But, the lowest levels of Cd are in control group, and those are statistically different from those of patients group (p≤0.01).

However, we did not determine any significant differences between all groups according to data of ACTH levels. The highest levels of ACTH have been determined in control group.

Levels of total T3 were higher in group of control than the levels of pre- and post-hemodialysis (p≤0.001). Comparing patients group before hemodialysis and after hemodialysis sessions, we reported that total T3 levels were higher in post-hemodialysis (p≤0.05). Whereas there were no differences between the levels of total T4 in post-hemodialysis and control group, the lowest levels have been determined in pre-hemodialysis and were statistically different from those of control and post-hemodialysis (p≤0.001).

Not only in post-hemodialysis but also in pre-hemodialysis group, a negative correlation between Cd and ACTH (respectively r= - 0.273, r= - 0.261) and between Cd and total T4 (respectively r= - 0.243, r= - 0.096) were determined. But the correlations between the parameters were not statistically important (data were not shown in table).

Discussion

Nowadays, studies are different from each other in about alterations of levels of elements in hemodialysis patients. These differences can be attributed to variation of subjects' criteria, which included to the study (number of subjects, duration of dialysis range), of times of blood samples collections and especially of dialysis membrane. According to this variations, finding different results are natural and are not enough to clarify the effects of elements in hemodialysis patients during their treatments.

The concentration of several trace elements in end-stage renal failure patients is disturbed, and some of the trace metals under study might share pathway of absorption, distribution and accumulation[2].

One of the studies[9], about the Cd metabolism in hemodialysis patients, states that alterations in Cd levels are important in evaluation of the hemodialysis patients' treatment. The researchers studied on hemodialysis patients who were received maintenance hemodialysis for at least 3 months. The whole blood levels of Cd had been determined as 3.32±1,49 µg/l in patients and as 1.14±0.62 µg/l in healthy people (p<0.0001)[9]. In previous study[17] the researchers concluded that serum Cd concentrations were higher in group of hemodialysis than control group (p<0.001). Determining high levels of Cd in patients pre and post-dialysis in our study cause an agreement on notice of importance of Cd levels in hemodialysis patients with study of Lee et al[9] and Turan et al[17].

Our findings show that levels of Cd in group of hemodialysis and control group are consistent with Kazi et al[1]'s data. The researchers showed that Cd concentrations were higher in group HD before hemodialysis (0.62±0.12 µ/l) and afer hemodialysis (0.40±0.15 µ/l) than control group (non-smokers 0.14±0.08, smokers 0.24±0.14 µ/l).

However, Malecka et al[10] confirmed that hemodialysis patients, who were dialyzed with cuprophan dialyzer, did not significantly demonstrate any alterations in serum Cd concentration. So that, those results are not similar with our data. But in their other research Malecka et al[18] observed that during hemodialysis session serum Cd levels increased significantly, when they compared two samples, which were taken during the dialysis session in different times. We can say that the contradiction between the results may be attributed to differences of variation of dialysis membrane as Padovese et al.[19] mention that the type of dialytic treatment could play a role in determining the effective amounts of the elements, which are transferred from the dialysis fluid into the patient's body.

These decreased Cd levels may be related to nutritional intake, intestinal uptake and altered distribution and in addition, protein-bound trace elements may be lost more readily in the presence of proteinuria[3].

There are some studies[20,21], which have been focused on the levels of ACTH in hemodialysis patients. Letizia et al.[21], determined an unimportant differences between the levels of healthy group and of pre dialysis of ACTH and a significant high ACTH levels in post dialysis comparing with the levels of pre dialysis. Dolinska-Laskos et al.[20] noticed on the influence of long-term dialysis therapy on the pituitary-adrenal axis functions. They determined that patients dialyzed longer than 100 months showed significantly high ACTH levels than controls. It has been found that CRF patients had significantly greater plasma ACTH levels than controls. Our results are not similar with those results[20-21]. We did not determine significant differences between the groups according to criteria of our patients. Therefore, we conclude that there is no influence of dialysis therapy on the pituitary-adrenal axis functions.

The patients with CRF may be in a sub clinical hypothyroid state, although hemodilution has been seen to have a strong effect on the thyroid hormone concentrations[22]. Our data concerning to total T3 levels are consistent but, total T4 levels in post-hemodialysis and control group are inconsistent with the result of Sakurai et al[22].

Xess et al.[23] presumed that patients showed significant decreases in T3 and T4 levels and serum levels of most hormones were altered because of several interplaying mechanisms. Our data concerning to total T3 and total T4 are similar with Xess et al.[23]. Meanwhile, Lim[15] suggests that the low thyroid state in uremia serves to defend against protein wasting and that misguided attempts to repletion thyroid hormone stores may worsen protein malnutrition.

As a result, data of Cd and ACTH and thyroid levels show that there are no relationships between each other. So that, when we focus on our data in the relation between ACTH and Cd, cannot cause an agreement on notice of relations of those parameters with the confirmation of Mgbonyebi et al.[12-13]. The researchers mentioned that Cd toxicity in adrenal functions caused hyperactivity in ACTH stimulation and expression[12-13].

In the face of the statistical significance of Cd, we can say that,

Table 1. The levels of parameters in control and patients group before dialysis (pre-hemodialysis) and after dialysis (post-hemodialysis)

Parameters	GROUPS			P VALUES		
	Control Group (A)	Pre- hemodialysis (B)	Post-hemodialysis (C)	A vsB	AvsC	BvsC
Cd (µg/dl)	0.14±0.06	0.22 ±0.03	0.24±0.05	0.007**	0.002**	0.315
ACTH(pg/ml)	44.21±8.67	37.74±3.44	34.77±3.42	0.563	0.344	0.592
Total T3(ng/dl)	92.53±3.94	59.03±2.02	65.70±2.50	0.000***	0.000***	0.034*
Total T4(µg/dl)	7.74±0.29	6.15±0.20	7.48±0.21	0.000***	0.416	0.000***

* P≤0.05 ; ** P≤0.01 ; *** P≤0.001

analyzing the levels of Cd may be important in monitoring hemodialysis patients' treatment. And also according to a study[24], Zinc (Zn) levels can be analyze with Cd levels because of the suggestion that iron deficiency increases the gastrointestinal absorption of Cd and Cd competes with zinc for binding sites on metallothionein which is important in the storage and transport of Zn during development. However, there are no associations between Cd and thyroid profiles, Cd and ACTH levels. Seen from this aspect, our study is not extensive to clarify the effects of trace elements in hemodialysis patients. The study is the first step to learn whether there are definite ratios of changes in the levels during the dialysis session. Therefore, our result may offer perspectives for future studies. Further extensive studies are necessary to clarify the effect of Cd levels alterations on hemodialysis patients' prognosis, which can be performed on a different method (analysis dialysis fluid in addition to blood samples, more numbered patients and collecting samples in different times of dialysis session, etc.).

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References

1. Kazi TG, Jalbani N, Kazi N, Jamali MK, Arain MB, Afridi HI et al. Evaluation of Toxic Metals in Blood and Urine Samples of Chronic Renal Failure Patients, before and after Dialysis. Renal Failure 2008; 30:737-745.
2. D'Haese PC, Couttenye MM, Lamberts LV, Elseviers MM, Goodman WG, Schrooten I, et al. Aluminum, iron, lead, cadmium, copper, zinc, chromium, magnesium, stronsium, and calcium content in bone of end-stage renal failure patients. Clin Chem 1999; 45:1548-1556.
3. Vanholder R, Cornelis R, Dhondt A, Lameire N. The role of elements in uraemic toxicity. Nephrol Dial Transplant 2002;17(suppl 2):2-8.
4. Hsu WA, Lee KC, Lin SL, Lee SH, Hsieh SJ, Kan YT. Clinical manifestations of trace metal abnormality in hemodialysis patients: A multicenter collaborative. Dial & Trans 1997;26:15.
5. Jin T, Lu J, Nordberg M. Toxicokinetics and biochemistry of cadmium with special emphasis on the role of metallothionein. Neurotoxicology 1998;19:529-535.
6. Andaç M, Say R, Denizli A. Molecular recognition based cadmium removal from human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2004; 811(2):119-126.
7. Hellstrom L, Elinder CG, Dahlberg B, Lundberg M, Jarup L, Persson B et al. Cadmium exposure and end-stage renal disease. Am J Kidney Dis 2001; 38:1001-1008.
8. Miccadei S, Floridi A. Sites of inhibition of mitochondrial electron transport by cadmium. Chem Biol Interact 1993;89:159-167.
9. Lee SH, Huang JW, Hung KY, Leu LJ, Kan YT, Yang CS. Trace metals' abnormalities in hemodialysis patients: Relationship with medications. Artif Organs 2000;24:841-844.
10. Malecka J, Grzeszczak W, Zukowska-Szcechowska E, Jendryczko A, Baczynski R. Does multiple use of a cuprophan dialyser influence levels of chromium and cadmium during hemodialysis in patients with chronic kidney failure? Pol Arch Med Wewn 2000;6:482-487.
11. Mehta HJ, Joseph LJ, Desai KB, Mehta MN, Samuel AM, Almeida AF et al. Total and free thyroid hormone levels in chronic renal failure. J Postgrad Med 1991;37:79-83.
12. Mgbonyebi OP, Smothers CT, Mortek JJ. Modulation of adrenal cell functions by cadmium salts:1.cadmium chloride effects on basal and ACTH-stimulated steroidogenesis. Cell Biol Toxicol 1993;9:223-234.
13. Mgbonyebi OP, Smothers CT, Mortek JJ. Modulation of adrenal cell functions by cadmium salts:2. sites affected by CdCl2 during unstimulated steroid synthesis. Cell Biol Toxicol 1994;10:23-33.
14. Lebkowska U, Malyszko J, Mysliwiec M. Thyroid function and morphology in kidney transplant recipient's hemodialyzed and peritonealy dialyzed patients. Transplant Proc 2003;35:2945-2948.
15. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis 2001;38:S80-84.
16. Kutlay S, Atli T, Koseogullari O, Nergizoglu G, Duman N, Gulu S. Thyroid Disorders in Hemodialysis Patients in an Iodine-deficient Community 2005;29(4):329-332.
17. Turan B, Delilbasi E, Dalay N, Sert S, Afrasyap L, Sayal A. Serum selenium and glutathione-peroxidase activities and their interaction with toxic metals in dialysis and renal transplantation patients. Biol Trace Elem Res 1992;33:95-102.
18. Malecka J, Grzeszczak W, Zukowska-Szcechowska E, Jendryczko A, Baczynski R. Levels of cadmium in serum of patients with chronic kidney failure. Przegl Lek 1994;51:291-295.
19. Padovese P, Galieni M, Brancaccio D, Pietra R, Fortaner S, Sabbioni E et al. Trace elements in dialysis fluids and assessment of the exposure of patients on regular hemodialysis, hemofiltration and continuous ambulatory peritoneal dialysis. Nephron 1992;61:442-448.
20. Dolinska-Laskos C, Grzeszczak W, Zukowska-Szczechowska E. Influence of long-term dialysis therapy on function of the pituitary-adrenal axis in patients with chronic renal failure. Pol Arch Med Wewn 1993;4:275-285.
21. Letizia C, Mazzafero S, De Ciocchis A, Cerci S, Morabito S, Cinotti GA et al. Effects of hemodialysis session on plasma beta-endorphin, ACTH and cortisol in patients with end-stage renal disease. Scand J Urol Nephrol 1996;30:399-402.
22. Sakurai S, Hara Y, Miura S, Urabe M, Inoue K, Tanikawa T et al. Thyroid functions before and after maintenance hemodialysis in patients with chronic renal failure. Endocrinol Japon 1988;35:865-876.
23. Xess A, Gupta A, Kumar U, Sharma HP, Prasad KM. Evaluation of thyroid hormones in chronic renal failure. Indian J Pathol Microbiol 1999;42:129-133.
24. Goyer RA. Nutrition and metal toxicity. Am J Clin Nutr 1995;61:646S-650S.